HA as a non-invasive marker for prognosis in patients with chronic liver disease of varying aetiology.

P07 SOCIO-DEMOGRAPHIC AND BEHAVIOURAL DETERMINANTS OF ABNORMAL LIVER FUNCTION IN A MULTI ETHNIC POPULATION IN THE UK: THE LOLIPOP STUDY

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[1]S D S Fraser, [1]J Parkes, [1]P J Roderick, [2]J S Kooner, [2]J Chambers. *[1]University of Southampton, UK; [2]Imperial College, London, UK*

Introduction Fatty liver disease (FLD) is common, with an estimated prevalence between 10 and 24% of the general population. Most patients are asymptomatic, and identified via incidental abnormal liver function tests, particularly alanine transaminase (ALT) and γ-glutamyltransferase (GGT). There are few population data on the prevalence or determinants of abnormal liver function.
Aim To determine the characteristics and associations of people with elevated values 1.5 times normal of both ALT and GGT in a population sample (upper limit of normal (ULN)=ALT ♂37 ♀31 IU/l; GGT ♂55 ♀38 IU/l) as an indicator of FLD.
Method The London Life Sciences Prospective Population Study (LOLIPOP study) is a population based cohort study of cardiovascular risk and outcomes in west London, an area with a high ethnic minority population. Adults aged 35–74 from 58 general practices were invited to cardiovascular screening which included questionnaire, clinical measurement and blood sampling. Response rate was 62%. Cross sectional data were obtained on 31 507, European white (n=9222), Indian Asian (n=19 769) and Black (n=2516). ALT and GGT were measured from a single serum sample. To identify key socio-demographic variables and potentially modifiable lifestyle factors, including BMI and alcohol intake, we used logistic regression models examining associations with elevated ALT and GGT.
Results The number with GGT and ALT measures was 31 465 (99.9% of total). The prevalence of elevated GGT above 1.5 times the ULN (GGT 1.5) was 10.4% (3265/31 465), for ALT 8% (2517/31 465) and for both 3.2% (996/31 465). 40% of those with ALT1.5 had GGT1.5, and 32% of those with GGT 1.5 had ALT 1.5. The independent odds of having both raised were increased in: younger people (OR 3.00 (95% CI 2.28 to 3.94) for 35–44 compared to 65–74 age group), south Asians (OR 1.29 (95% CI 1.10 to 1.51) compared to White), greater alcohol intake (OR 6.52 (95% CI 5.36 to 7.95) for >28 units per week compared to no alcohol), raised BMI (OR 2.34 (95% CI 1.94 to 2.83) obese compared to normal), and diabetes (OR 1.32 (95% CI 1.07 to 1.63), with a dose related gradient for alcohol consumption. Gender, deprivation, and taking statin were not significantly associated, and no interaction observed between alcohol and gender or BMI.
Conclusion The prevalence of abnormal liver function tests, suggesting FLD, was common (directly standardised prevalence of 3.3% in this age group in the England and Wales population). BMI, and alcohol independently increased risk across the range of their values, highlighting the importance of considering both in preventing severe liver disease and counselling patients.

P08 SPONTANEOUS BACTERIAL PERITONITIS PROPHYLAXIS: REDUCING THE INCIDENCE OF C DIFFICILE INFECTION

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[1]H Jafferbhoy, [1]M H Miller, [1]C Shekar, [2]M Lockhart, [1]J F Dillon. *[1]GUT Group Biomedical Research Institute, Dundee University; [2]Department of Microbiology, Ninewells Hospital*

Introduction Spontaneous bacterial peritonitis is a serious and life-threatening complication of cirrhosis, especially common in hospitalised patients. Antibiotic prophylaxis is effective but can lead to an increased incidence of hospital-acquired infections such as *Clostridium difficile*.
Aim We evaluated whether two alternative prophylaxis agents were equally efficacious in preventing SBP, and the impact on risk of *C difficile* infection.
Method A consecutive, cohort study of hospitalised patients with cirrhosis and ascites, over a 3-year period in a tertiary hospital. In the first cohort (2007–2009), ascitic patients requiring prophylaxis received Norfloxacin 400 mg/d during their hospital admission. In the second cohort (2009–2010) patients received prophylactic Co-trimoxazole 960 mg/d during their hospital admission. Data were extracted by case note review and the two cohorts compared.
Results 174 patients admitted during 2007–2010 accounted for 231 hospital episodes with ascites. The Norfloxacin group had 154 episodes and the Co-trimoxazole group had 77. The mean age of the cohort was 57.4 years (SD 12.4) and 62% were male. Alcoholic cirrhosis was the major aetiology accounting for 79% of cases. The mean Child-Pugh and UKELD scores were 10.7 and 54 respectively. The overall incidence of SBP in our cohort was 19%. Abstract P08 table 1 demonstrates that the incidence of hospital acquired SBP, prophylaxis failure and mortality was not statistically different between the two therapies. However, selective bowel sterilisation with Co-trimoxazole did not lead to an increase *C difficile* infection rate.

Abstract P08 Table 1 Outcome of patients hospitalised with cirrhosis and ascites

	Norfloxacin	Co-trimoxazole	p Value
Episodes*	134	67	
Hospital acquired SBP	9 (6.71%)	7 (10.44%)	NS
Prophylaxis failure %	5/130 (3.84%)	4/64 (6.24%)	NS
C difficile rate %	13 (9.7%)	0	0.009
30-day mortality %	25 (18.65%)	15 (22.38%)	NS
90-day mortality %	41 (30.59%)	16 (23.88%)	NS

*Excluding patients with community acquired SBP.

Conclusion Survival of cirrhotic patients with ascites is inversely related to severity of Liver disease, worsened with development of infections such as spontaneous bacterial peritonitis and *C difficile*. This study shows that Co-trimoxazole inpatient prophylaxis against SBP is as effective as quinolone based regimes, but has the advantage of a dramatic reduction in *C difficile* infection. At the same time the importance of measures like hand hygiene compliance, environmental cleanliness and strict policy of in hospital antibiotic prescribing cannot be underestimated.

P09 VALIDATION OF A NOVEL BIOMARKER MODEL FOR THE PREDICTION OF NON-ALCOHOLIC STEATOHEPATITIS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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[1]S Tanwar, [2]P Trembling, [3]I N Guha, [4]J Parkes, [5]P Kaye, [6]A D Burt, [7]S D Ryder, [4]G P Aithal, [8]C P Day, [9]W M Rosenberg. *[1]Centre for Hepatology, University College, London, UK; [2]Centre for Hepatology; [3]University College London; [4]UK; [5]University Hospital; [6]Queen's Medical Centre; [7]Nottingham; [8]Public Health Sciences and Medical Statistics; [9]University of Southampton*

Introduction The detection of non-alcoholic steatohepatitis (NASH) within non-alcoholic fatty liver disease (NAFLD) is important both

Abstract P09 Table 1

	Training cohort AUROC (95% CI)	Validation cohort AUROC (95% CI)
NAS 0–2 vs NAS 3–8	0.833 (0.700 to 0.966)	0.829 (0.737 to 0.921)
NAS 0–3 vs NAS 4–8	0.854 (0.763 to 0.945)	0.784 (0.668 to 0.900)
NAS 0–4 vs NAS 5–8	0.865 (0.772 to 0.957)	0.723 (0.505 to 0.941)

for ascertaining prognosis and the stratification of patients for existing interventions and emerging therapies. Liver biopsy is considered the reference standard for assessing NASH. The aim of this study was to develop a biomarker of NASH which would be able to detect NASH prior to the development of significant hepatic fibrosis. Candidate biomarkers of hepatic inflammation, apoptosis and liver fibrosis were selected on the basis of biological plausibility and previous association with NAFLD.

Method 172 patients with NAFLD and no evidence of other liver disease were consecutively recruited from two centres. 84 patients from the first centre were included as a training cohort and 88 patients from the second centre as a validation cohort. Liver biopsies were performed on all patients and scored using the NAFLD activity score (NAS). 36 patients with advanced fibrosis were excluded from the analysis. Serum samples were taken on all patients and tested for five matrix proteins (HA, P3NP, TIMP-1, Procollagen 4 and YKL-40) and 19 haematological and biochemical parameters including HOMA-IR. Stepwise multiple linear regression was used to determine the relationship of the multiple variables to the NAS score.

Results A model combining terminal peptide of pro-collagen III (P3NP) and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) was found to significantly correlate with the NAS score in the training cohort ($R=0.643$, $R2=0.413$, $p<0.0000001$). The regression model was then validated in the second patient cohort. AUROC were calculated for the ability of the model to discriminate between differing degrees of NAS.

Conclusion This model appears to have good diagnostic performance for the detection of NASH in both the training and validation cohorts. Our results appear promising and if confirmed in further studies this model will be of clinical utility in detecting the minority of patients with NAFLD who have NASH and are at risk of developing progressive liver disease.

P10 WHOLE-EXOME-SEQUENCING-BASED DISCOVERY OF NOVEL SYNDROMIC FORM OF NEONATAL CHOLESTASIS

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[1]J L Hartley, [2]M Simpson, [3]L Tee, [4]R M Brown, [5]S Kirkham, [3]S Pasha, [2]R C Trembath, [3]P Gissen, [3]E R Maher, [1]D A Kelly, [3]N V Morgan. *[1]Birmingham Children's Hospital; [2]King's College Hospital, London; [3]Birmingham University; [4]University Hospitals Birmingham; [5]Queen's Medical Centre, Nottingham*

Introduction Two cousins from a consanguineous family presented with low γ glutamyl transferase (GGT) cholestasis, trichorrhexis nodosa (TN) and severe hypoglycaemia which required diazoxide to stabilise. One child also had life threatening diarrhoea necessitating parenteral nutrition, which suggested the possible diagnosis of trichohepatoenteric syndrome (THES). However screening of the THES gene (*TTC37*) excluded mutations.

Aim The aim of this study was to identify the molecular genetic defect in this family and hence further understanding of unexplained cholestasis within a multisystem disorder.

Method We used a novel combination of autozygosity mapping combined with whole-exome-sequencing (WES). An Affymetrix 250K SNP chip genome-wide linkage scan was used to identify common regions of shared homozygosity. SureSelect human All Exon kit (Agilent Technologies) and Illumina GaIIx was used for WES of both individuals. Single nucleotide substitutions and small insertion deletions were identified. Filtering of variants for novelty was performed by comparison to dbSNP131 and 1000 Genomes pilot SNP calls (March 2010) and variants identified in 40 control exomes sequenced and analysed by the same method described above.

Results The largest overlapping autozygous regions were at chromosome 7, 16, 20, 12 and 4. The whole exome sequencing identified 17 844 and 17 867 variations in patients 1 and 2 respectively. Of these only three homozygous non-synonymous variants and one frameshift variant were found in both patients in the identified homozygous regions. The frameshift was a homozygous single base G deletion (c.587delG) in exon 6 of *AKR1D1* which mapped within the candidate homozygous region in chromosome 7. The variant results in a frameshift at amino acid 196 leading to a premature stop codon 11 amino acids downstream (p. Cys196SerfsX11).*AKR1D1* encodes the enzyme δ^4-3-oxosteroid 5β-reductase that is required for the synthesis of chenodeoxycholic and cholic acids important for normal bile flow. Mutations in *AKR1D1* have previously been described in patients with severe neonatal liver disease.

Conclusion In conclusion we have extended the clinical features of bile salt synthesis disorders resulting from mutations in *AKR1D1* to include a severe form of low GGT cholestasis, TN and severe hypoglycaemia which may be amenable to treatment with bile salt supplementation. Combining the technique of whole genome linkage mapping and WES creates a powerful tool to elucidate the molecular basis of uncharacterised genetic disorders.

P11 INDUCTION OF HYPERAMMONAEMIA FROM THE SMALL AND LARGE INTESTINE IN PATIENTS WITH CIRRHOSIS WITH MAGNETIC RESONANCE QUANTIFICATION OF BRAIN WATER AND METABOLITES

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[1]H Mardini, [1]F Smith, [2]A Blamirel, [2]C Record. *[1]Royal Victoria Infirmary, Newcastle Upon Tyne and Institute of Cellular Medicine, Newcastle University; [2]Newcastle Magnetic Resonance Centre, Newcastle University, UK*

Introduction Induction of hyperammonaemia from glutaminase action in the small intestine[1] or systemic catabolism of oral amino acids[2 3] is well recognised but, although suggested in 1959 by Walser and Bodenlos,[4] ureolysis resulting in hyperammonaemia has not been demonstrated from urea delivered to the colon. Hepatic encephalopathy (HE) is now thought to be caused by cerebral oedema.

Aim We hypothesised that if hyperammonia is a key factor in hepatic encephalopathy, induced hyperammonaemia from oral amino acid or urea challenge would lead to transient changes in brain water distribution and metabolite concentration.

Method Amino acid (mixture of equal parts of glycine, serine and threonine) or urea challenges were undertaken in 18 patients with stable cirrhosis 5 of whom gave a history of hepatic encephalopathy. Sequentail blood ammonia concentration was determined with the ammonia checker and brain water and metabolites with magnetic resonance diffusion tensor imaging and spectroscopy.

Results Oral urea and amino acids (delivered to the colon by coating) resulted in peak increments in blood ammonia of 146±SD 164 and 55±51 μmol/l while for uncoated amino acids the mean increment was 58 (±41) μmol/l. The latter was accompanied by a significant increase in ADC of 9% ($p=0.004$). Increased ADC was significantly correlated with blood ammonia ($r=0.58$, $p=0.04$). The change in ammonia levels also correlated with the increase in